



The US Tox21 Collaboration: Advances Made and Lessons Learned

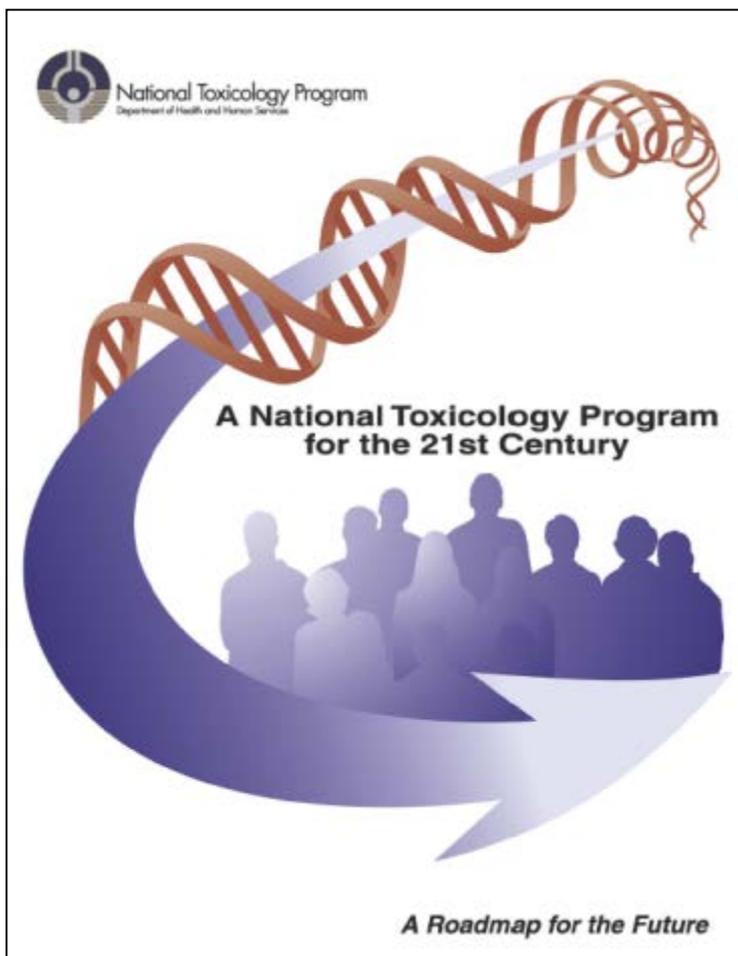
Chairpersons: Linda Birnbaum, NIEHS and NTP
Robert Kavlock, US EPA/ORD

Monday, March 23, 2015

9:15 am – 12:00 noon

CC Ballroom 6E

2004 NTP Vision and Roadmap for the 21st Century

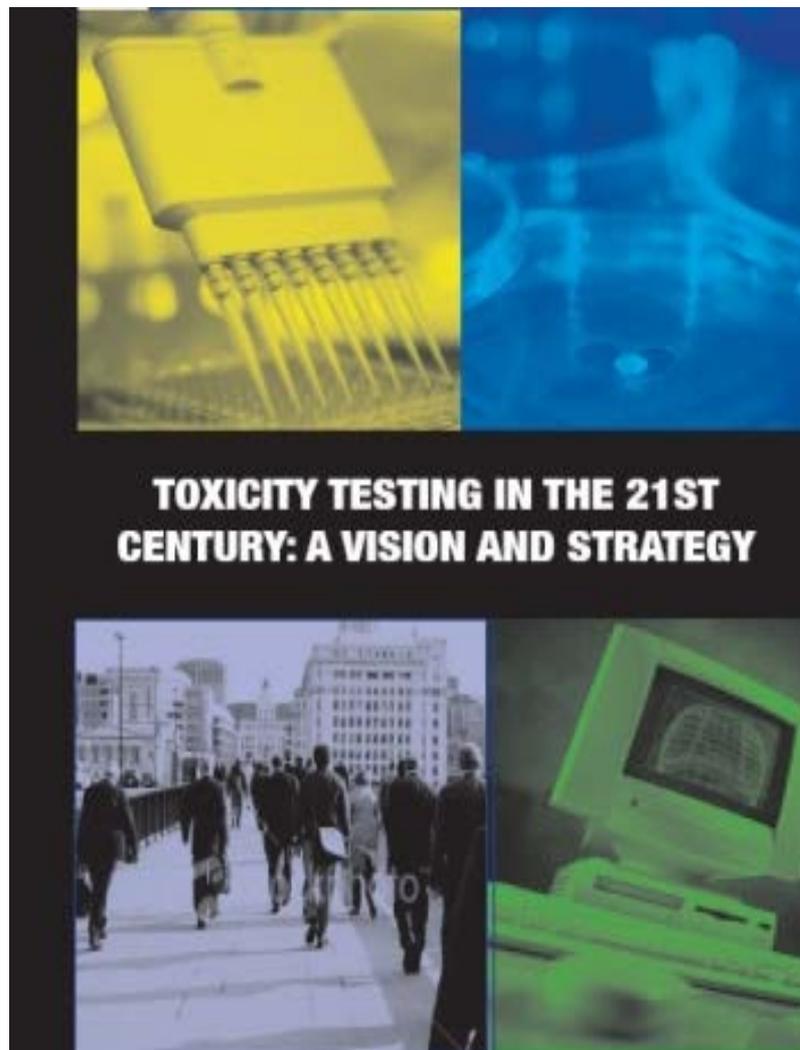


To meet the challenges of 21st century toxicology, the 2005 NTP Roadmap included a major initiative to develop a high throughput screening (HTS) program with 3 main goals:

- To prioritize chemicals for further in-depth toxicological evaluation.
- To identify mechanisms of toxicity (*characterize toxicity pathways, facilitate cross-species extrapolation, provide input to models for low-dose extrapolation*).
- To develop predictive models for *in vivo* biological response in humans.

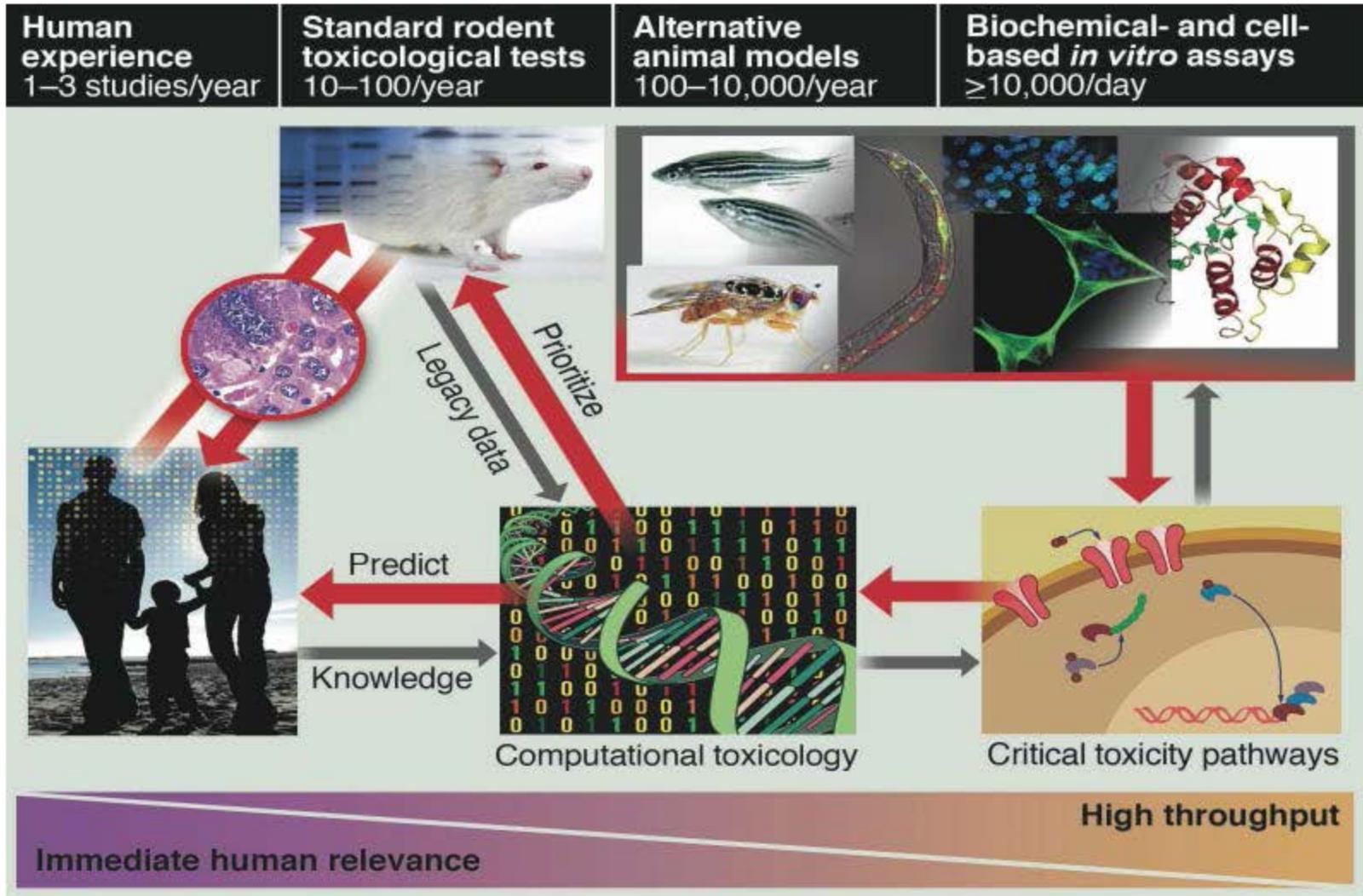
Toxicity Testing in the 21st Century

2007 National Academy of Science Report



Envisions a **not-so-distant future** in which virtually all routine toxicity testing would be conducted *in vitro* in **human cells** or cell lines by evaluating **perturbations of cellular responses** in a **suite of toxicity pathway assays** using **high throughput robotic assisted methodologies**.

Transforming Environmental Health Protection





Formation of the Tox21 Program

- 5-year Memorandum of Understanding (MoU) on “High-Throughput Screening, Toxicity Pathway Profiling, and Biological Interpretation of Findings”.
- Released on Feb 14, 2008, signed by NHGRI (F.S. Collins), NIEHS/NTP (S.H. Wilson), and EPA (G.M. Gray).



- Revised 5-year MoU to add FDA signed on July 19, 2010, by NHGRI (E.D. Green), NIEHS/NTP (L.S. Birnbaum), EPA (P.T. Anastas), and FDA (J. Woodcock).
- Known informally as Tox21 for Toxicology in the 21st Century.



Purpose of Tox21: Bringing a New Era in Toxicology



Support the evolution of toxicology from a mostly observational science to a predominantly predictive science focused upon mechanism-based, biological observations using cultured cells, model tissues, and lower organisms.



Tox21 Goals

- Research, develop, validate, and translate new chemical testing methods that characterize toxicity pathways.
- Use new technologies to develop models that can be used to more effectively predict how chemicals will affect biological responses.
- Gain better understanding of the relationship between chemicals and human diseases, in order to:
 - Prioritize compounds for more comprehensive testing.
 - Identify mechanisms of action.
 - Develop predictive models of human disease.





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- Rusty Thomas, US EPA - *The US EPA ToxCast Program: Moving from Data Generation to Application.*
- Anton Simeonov, NCATS - *Tox21 Phase II: Testing the 10K Library in Quantitative High-Throughput Screening Assays.*
- Rick Paules, DNTP/NIEHS - *Tox21 Phase III: Improving on Biological Coverage, Relevance, and Public Outreach.*
- Warren Casey, DNTP/NIEHS - *Prioritization and Predictive Toxicology: Estrogen Receptor Active Compounds.*
- Tina Bahadori, US EPA - *From Data to Decisions—An End User's Perspective.*

Tox21's Unique Capabilities



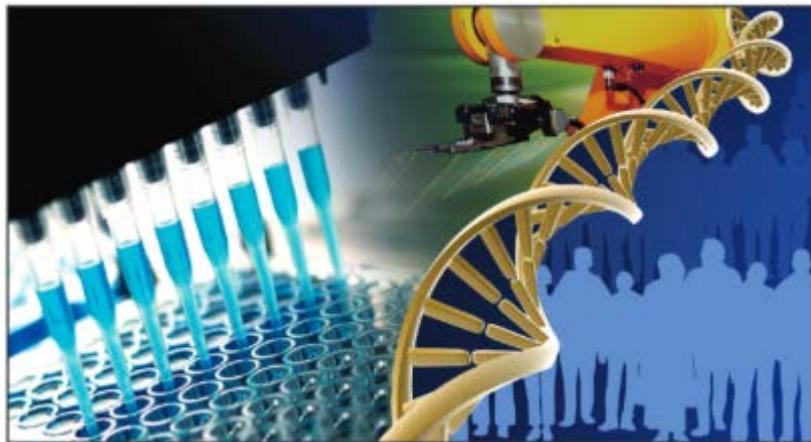
- Unique capabilities not currently available elsewhere:
 - Robotics.
 - High throughput screening platform.
 - Compound handling capabilities.
 - Informatics tools.
- In the past 2 years, NCATS has been screening more than 10,000 compounds chosen jointly by the NTP, NCATS, and EPA against a set of key nuclear receptors and stress response pathways using cell-based assays.
- This screening, still in progress, has greatly advanced our understanding of the potential toxicity of many substances of concern.

Tox21's Next Phase – Improving Coverage & Relevance



- Increased use of computational models to predict toxicity and metabolism.
- Increased focus on human cells with known ability to metabolize chemicals
- Expand our understanding of biology by developing and implementing a high throughput and low cost approach to measure the expression level of all genes in a cell at once – **Toxicogenomics**
- Increase use of stem cells (both embryonic and iPS) to investigate the effects of chemicals on developmental processes
- Increased focus on genetic variation to understand susceptibilities - **Toxicogenetics**

NIEHS-NCATS-UNC DREAM Toxicogenetics Challenge



<https://www.synapse.org/#!/Challenges:DREAM8>

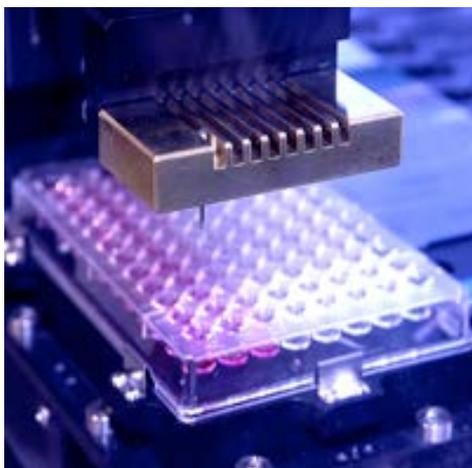
- An innovative crowdsourced computational challenge launched on June 11, 2013, and closed September 15, 2013.
- The NIEHS-NCATS-UNC team conducted the largest ever population-based *in vitro* cytotoxicity study:
 - 1086 cell lines representing 9 distinct geographical populations.
 - 179 drugs and environmental chemicals.
- The challenge asked participants to build models based on data from the toxicogenetics project to predict:
 1. The toxic response of individuals to chemicals.
 2. How a particular population will respond to certain types of chemicals.

Benzene Inhalation Study with the DO Mouse

- Diversity outbred (J:DO) male mice selected from 175 breeding pairs
- Dose levels: 0, 1, 10, 100 ppm benzene, 28 days, 6 hr/day
- 600 mice total: 2 separate cohorts to assess reproducibility
- Endpoints for hematotoxicity and genetic damage
 - % reticulocytes and micronucleated reticulocytes in bone marrow and blood
 - Mouse Universal Genotyping Array (7.5K SNPs; MUGA)
 - Mapping & Linkage analysis (QTLRel)
- Mice showed a 205-fold difference in susceptibility
- Associated with variable expression of a sulfotransferase detoxification enzyme



Milestones of Tox21



- Made all Tox21 Phase I and Phase II data collected to date public.
- Made chemical libraries available to investigators to expand the breadth of toxicological information.
- Identified artifacts in high throughput screening data that lead to false results.
- Made progress in data analysis and development of tools for prioritizing chemicals for more extensive testing using traditional methods.
- Exchanged assays and data with other organizations/efforts (e.g., EU Joint Research Centre, Health Canada, SEURAT, OpenTox).
- Worked with other NIEHS groups to evaluate Tox21 data for use by regulatory agencies.

Benefits of Tox21

- Information and informatics tools from Tox21 will facilitate new drug discovery and promote translational research across NIH by eliminating substances with undesirable effects from further development.
- This federal multiagency collaboration is realizing a new vision for toxicological testing and contributing to improving public health.

